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10/084,632	02/25/2002	Timothy W. Starzl	4724-2	6303

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EXAMINER

LUM, LEON YUN BON

ART UNIT PAPER NUMBER

1641

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/084,632

Applicant(s)

STARZL ET AL.

Examiner

Leon Y. Lum

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 June 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 June 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

AD

DETAILED ACTION

1. The amendment filed 13 June 2005 is acknowledged and has been entered.

Drawings

2. The drawings were received on 13 June 2005. These drawings are acceptable.

Specification

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

4. The abstract of the disclosure is objected to because line 4 contains the legal phrase "herein" and line 5 contains the legal phrase "thereto". Correction is required.

See MPEP § 608.01(b).

Claim Objections

5. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

There are currently two claims that are numbered "15". The second claim is considered to be misnumbered. Misnumbered claims 15-18 have been renumbered 16-19.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 17, which has been renumbered (see Claim Objection section above) from incorrectly numbered claim 16, is vague and indefinite. The claim indicates an amendment made to the claim, as shown by the underlined "6". However, the claim status identifier states that the claim is an original claim, and the original claim as filed is

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dependent on claim 1. Therefore, it is unclear whether the claim is intended to be dependent upon claim 16 or claim 1, since the amendment and status identifier are in conflict. In the event that the instant claim is intended to be dependent upon claim 16, a new matter situation may occur.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-4, 8, 14, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (Biotechnic & Histochemistry, 1995, vol. 70, no. 4, pages 211-216) in view of Stimpson et al (US 5,599,668).

Gao et al reference teaches a method for analyzing a sample for binding events when a substance of interest is present with the sample, comprising establishing at least one of a setting and a position for an instrument that includes a control and that is involved with making determinations related to at least the presence of the substance of interest with the sample, positioning the sample relative to a light source that outputs a light beam, receiving said light beam by at least portions of the sample, collecting scattered light from the sample portions using a light collection device of said instrument, and processing digital image data based on said light collected during said collecting step using said control of said instrument, by disclosing the principle of epipolarization microscopy for the detection of a sample (Figures 1 and 5, and captions), wherein the detectable signal depends on the amount of adsorbed streptavidin-silver enhanced gold that gives off a certain intensity (page 215, left column, 1st full paragraph; and Figure 4 and caption).

However, Gao et al reference fails to teach the step of counting objects after said processing step using digital information in determining at least whether the substance of interest is present with the sample.

Stimpson et al reference discloses image processing of an assay for quantitative results to determine the level of binding pair members present in a fluid sample, wherein the image processing is performed on images of scattered light detected using a CCD (column 21, line 50 to column 22, line 65, especially column 21, lines 51-54 and column 22, lines 3, 20-22, 34-37, and 50-56), in order to detect one or more specific binding analytes, especially DNA or oligonucleotides, for sequencing purposes (column 1, lines 7-14 and column 3, lines 42-49).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Gao et al with the step of image processing of an assay for quantitative results to determine the level of binding pair members present in a fluid sample, wherein the image processing is performed on images of scattered light detected using a CCD, as taught by Stimpson et al, in order to detect one or more specific binding analytes, especially DNA or oligonucleotides, for sequencing purposes. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in including image processing to obtain quantitative results, as taught by Stimpson et al, in the method of Gao et al, since Gao et al teach light scatter detection using CCD devices, and the image processing taught by Stimpson et al is performed on scattered light detected by a CCD device.

With regards to claim 2, Gao et al reference teaches that said establishing step includes providing magnification related to collecting said scattered light, by disclosing that samples were evaluated using a 10 X objective lens (page 214, left column, 2nd paragraph, lines 1-6).

With regards to claims 3-4 and 8, Gao et al reference teaches that said establishing step includes locating an optical subsystem in a direction relative to the sample (claim 3), locating said light source such that said light beam is at a desired angle relative to the sample (claim 4), and that said processing step includes receiving electrical signals from said light collection device and obtaining said image data using said electrical signals (claim 8), by disclosing the tungsten light, filters, condenser, polarizer, dichrotic half-mirror, crossed-analyzer, diaphragm, mercury vapor lamp, CCD camera, and Image Processing Unit of an epipolarization microscopy, wherein the CCD camera is connected to the Image Processing Unit (Figure 5 and caption).

With regards to claim 14, Stimpson et al reference teaches the step of storing information in memory of said control related to said at least one of said setting and said position, by disclosing the digital information may be stored in RAM or any storage device for further manipulation (column 22, lines 20-22).

With regards to claim 17, Stimpson et al reference teaches that the substance of interest is a first substance of interest and said image data from said first subspot includes information related to the first substance of interest when present and said second subspot has a second sample, different from the first sample, to be used in determining whether a second substance of interest, different from the first substance of

interest, is present, by disclosing multiple capture sites on a support comprising a DNA array and collecting scattered light from each site, in order to measure binding of a light scattering label to simultaneously detect the presence of one or more specific binding analytes in a fluid sample through hybridization (column 3, lines 45-55 and 65-67; and column 4, lines 29-31).

With regards to claim 18, Gao et al reference teaches that said digital image is based on a two dimensional array of elements, by disclosing that the principle of epipolarization microscopy is performed with immunoassay on a microscope slide with 30 micro wells (page 211, left column, 1st paragraph to right column, 2nd paragraph). With regards to claim 19, Gao et al reference teaches that the sample has a light-scattering label that includes colloidal gold, by disclosing colloidal gold conjugated to streptavidin that is immobilized to a biotin, which is bound to a secondary antibody that is attached to an antigen (Figure 1 and caption).

13. Claims 5, 9-13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (Biotechnic & Histochemistry, 1995, vol. 70, no. 4, pages 211-216) in view of Stimpson et al (US 5,599,668) as applied to claim 1 above, and further in view of De Brabander (The Amer. J. Anat., 1989, vol. 185, pages 282-295).

Gao et al and Stimpson et al references have been disclosed above and Gao et al reference additionally teaches that said collection device includes a photoelectric device, by disclosing the CCD camera and Image Processing Unit, as stated above (Figure 5 and caption). However, Gao et al and Stimpson et al references fail to teach

that said establishing step includes regulating a gain related to said photoelectric device to provide desired light contrast (claim 5) and adjusting a gain associated with said light collection device after conducting at least some of said processing step (claim 15).

De Brabander et al reference discloses the step of subtracting an equal amount of light from all pixels (increasing the offset) and expanding the remaining signal to the original value (increasing the gain), wherein a "mottle" image obtained with the preparation out of focus is stored in digital format in a frame memory and subtracted in real time from subsequent images, in order to produce an increase in intensity (contrast) to distinguish between gold particle markers and background signal, and increase the contrast of other elements that disturb the image, and to also improve visualization of contrast generated by the preparation itself (page 282, right column, 3rd paragraph to page 283, left column; and Figure 2 and caption).

It would have been obvious at the time of the invention to modify the method of Gao et al and Stimpson et al with the step of subtracting an equal amount of light from all pixels (increasing the offset) and expanding the remaining signal to the original value (increasing the gain), wherein a "mottle" image obtained with the preparation out of focus is stored in digital format in a frame memory and subtracted in real time from subsequent images, as taught by De Brabander, in order to produce an increase in intensity (contrast) to distinguish between gold particle markers and background signal, and increase the contrast of other elements that disturb the image, and to also improve visualization of contrast generated by the preparation itself. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in

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increasing the offset and gain of the image, as taught by De Brabander et al, in the method of Gao et al and Stimpson et al, since Gao et al and Stimpson et al teach image detection of light scattering from gold particles, and the image processing performed by De Brabander et al is conducted on images derived from gold particles.

With regards to claims 9-13, De Brabander et al reference teaches that said processing step includes using at least a first light intensity related procedure and at least a first size related procedure (claim 9), wherein said first light intensity related procedure includes performing a thresholding function related to light intensity (claim 10), said performing step includes using a histogram analysis (claim 11), wherein said first size related procedure includes filtering using at least one parameter related to size (claim 12), and said processing step includes providing a lower limit threshold based on histogram-related information (claim 13), by disclosing the step of first increasing the offset and then increasing the gain of pixels from an image, as stated above (page 282, right column, 3rd paragraph, lines 11-27; and Figure 2 and caption) wherein gold particles of 20-40 nm diameter provide sufficient contrast as individual units (page 284, left column, 1st paragraph), and a segmentation step based on pure gray-level information in a single pixel, wherein gold particles have significantly lower gray values than the background after 8-bit digitalization, and only gray levels lower than a certain threshold are retained to locate the gold pixels (page 286, right column, 4th paragraph to page 288, right column, last paragraph).

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14. Claims 6-7 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (Biotechnic & Histochemistry, 1995, vol. 70, no. 4, pages 211-216) in view of Stimpson et al (US 5,599,668) as applied to claim 1 above, and further in view of Oberhardt (US 6,251,615 B1).

Gao et al and Stimpson et al references have been disclosed above, but fail to teach that said light beam includes a laser beam and the sample is associated with a test spot and said establishing step includes having said laser beam encompass at least all of said test spot with uniform intensity (claim 6), said positioning step includes moving said light beam (claim 7), and the sample includes a test spot comprised of at least a first subspot and a second subspot immediately adjacent to said first subspot and in which said processing step includes obtaining said image data using said collection device from said first subspot, and separately obtaining said image data from said second subspot, and said counting step includes counting objects from said first subspot before obtaining said image data from said second subspot (claim 16).

Oberhardt reference teaches moving the microscope field from capture zone to capture zone on a surface, wherein a plurality of light sources, including epi-illumination and laser sources, provides illumination of the capture zones, and a CCD detector array connected to camera electronics and a computer images captured cells (column 25, lines 16-67, especially lines 16-28, 37-46, and 56-59; and Figure 12), and wherein as the microscope field moves systematically from section to section along the entire area of the upper surface of the chamber wall, a number of captured cells is counted such that a sequential interrogation is achieved and recorded (column 26, lines 19-22, 35-38,

and 50-63), in order to provide a convenient analysis of samples containing suspended cells for research and clinical use, including measuring the kinetics of cell capture (column 2, lines 24-45).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Gao et al and Stimpson et al with the step of moving the microscope field from capture zone to capture zone on a surface, wherein a plurality of light sources, including epi-illumination and laser sources, provides illumination of the capture zones, and a CCD detector array connected to camera electronics and a computer images captured cells, and wherein as the microscope field moves systematically from section to section along the entire area of the upper surface of the chamber wall, a number of captured cells is counted such that a sequential interrogation is achieved and recorded, as taught by Oberhardt, in order to provide a convenient analysis of samples containing suspended cells for research and clinical use, including measuring the kinetics of cell capture. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in moving the microscope field, using a laser source, and sequentially counting bound analytes, as taught by Oberhardt, in the method of Gao et al and Stimpson et al, since Gao et al and Stimpson et al teach the detection of scattered light using a CCD camera and quantification of detected objects by post-image capture analysis using a computer, and the steps of Oberhardt include the detection of scattered light using a CCD camera and counting captured analytes using computer processing.

Response to Arguments

15. On page 9, lines 3-5, of the Remarks, filed 13 June 2005, Applicants traversed the objection to the specification made in the previous Office Action by stating that the amendments as filed were proper. Upon further investigation, it has been determined that the amended specification did meet the proper requirements and the objection is hereby withdrawn.

16. Due to the claim amendments submitted 13 June 2005, the objections and rejections to claims 1-19 made under 35 U.S.C. 112, 2nd paragraph in the previous Office Action have been overcome.

17. On page 9, last paragraph to page 10, 3rd paragraph of the Remarks, Applicants argue that it would not have been obvious to combine the epipolarization microscopy of Gao et al with the light scattering techniques of Stimpson et al since the two references deal with fundamentally different imaging techniques. Specifically, Applicants state that Gao et al relies upon the detection of polarized light and Stimpson et al detects scattering of light from the surface of an evanescent waveguide.

Applicant's arguments have been fully considered but they are not persuasive. Applicants contend that Gao et al and Stimpson et al references each teach two different methods of light detection that are not obvious to combine. While the references do disclose separate methods of capturing light, this fact alone does not

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render the rejection made in the previous Office Action invalid since the references were not combined to integrate two different light detection methods. Gao et al reference was applied to teach all the limitations set forth in claim 1 except for the step of counting objections after digital information processing. Stimpson et al reference was thereby applied solely to teach the step of counting objects **after** image capture, and not to teach the detection step itself since this step had already been taught by Gao et al. Therefore, the argument that Gao and Stimpson describe two different light capture techniques does not carry any weight in traversing the reason and motivation set forth in the previous Office Action for combining the references. By teaching that one or more specific binding analytes can be detected for sequencing purposes, Stimpson et al provides proper motivation of applying image processing to the captured light of Gao et al. In addition, since Gao et al teach that light is captured using a CCD and Stimpson et al teach image processing of light captured using a CCD, there is reasonable expectation of success in combining Gao et al and Stimpson et al.

Therefore, Applicant's arguments are not convincing and the rejection under 35 U.S.C. 103(a) as set forth in the previous Office Action is maintained.

Conclusion

18. No claims are allowed.

19. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y. Lum whose telephone number is (571) 272-2878. The examiner can normally be reached on weekdays from 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leon Y. Lum
Patent Examiner
Art Unit 1641



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02/29/05